VERSION WITH MARKINGS TO SHOW CHANGES MADE

DO NOT ENTER

4. (Amended) A method of treating or preventing inflammatory processes and diseases as in Claims 1, 2, or 3 further comprising wherein said inhibitory compound is used in combination with one or more other therapeutically active agents under the following conditions:

A. where a joint has become seriously inflammed as well as infected at the same time by bacteria, fungi, protozoa, and/or virus, said inhibitory compound is administered in combination with one or more antibiotic, antifungal, antiprotozoal, and/or antiviral therapeutic agents;

B. where a multi-fold treatment of pain and inflammation is desired, said inhibitory compound is administered in combination with inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting ~~essentially~~ of:

1. NSAIDs;

2. H_1 -receptor antagonists;

3. kinin-B_1 - and B_2 -receptor antagonists;

4. prostaglandin inhibitors selected from the group consisting of PGD-, PGF- PGI_2 -, and PGE-receptor antagonists;

5. thromboxane A_2 (TXA2-) inhibitors;

6. 5- and 12-lipoxygenase inhibitors;

7. leukotriene LTC_4 -, LTD_4/LTE_4 -, and LTB_4 -inhibitors;

8. PAF-receptor antagonists;

9. gold in the form of an aurothio group together with one or more hydrophilic groups;

10. immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate;

11. anti-inflammatory glucocorticoids;

12. penicillamine;

13. hydroxychloroquine;

14. anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone, and benzbromarone;

C. where older dogs are being treated for disease conditions, syndromes and symptoms found in geriatric dogs, said inhibitory compound is administered in combination with one or more members independently selected from the group consisting ~~essentially~~ of:

1. cognitive therapeutics to counteract memory loss and impairment;

2. anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure, and myocardial infarction, selected from the group consisting of:

a. diuretics;

b. vasodilators;

c. β-adrenergic receptor antagonists;

d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;

e. angiotensin II receptor antagonists;

f. renin inhibitors;

g. calcium channel blockers;

h. sympatholytic agents;

i. α_2-adrenergic agonists;

j. α-adrenergic receptor antagonists; and

k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

3. antineoplastic agents selected from:

a. antimitotic drugs selected from:

i. vinca alkaloids selected from:

[1] vinblastine, and

[2] vincristine;

4. growth hormone secretagogues;

5. strong analgesics;

6. local and systemic anesthetics; and

7. H_2 -receptor antagonists, proton pump inhibitors, and other gastroprotective agents.

9. (Amended) A pharmaceutical composition according to Claim 8 wherein said dosage forms comprise one or more members selected independently from the group consisting ~~essentially~~ of suppositories; solid peroral dosage forms selected from the group consisting of delayed-release tablets, capsules, caplets, lozenges, troches, and multiparticulates; enteric-coated tablets and capsules which prevent release and absorption **of said anti-inflammatory selective COX-2 inhibitory compound** in the stomach of said member being treated to facilitate delivery **of said anti-inflammatory selective COX-2 inhibitory compound** distal to the stomach of said member; sustained-release oral tablets, capsules and microparticulates which provide systemic delivery of said inhibitor in a controlled manner over at least a 10-hour period; a chewable or ingestible oral tablet; a

unit dose packet sachet, a suspension made from said unit dose packet sachet, a powder for oral suspension, or an oral suspension ~~per se~~; a fast-dissolving tablet; encapsulated solutions; an oral paste; a granular form incorporated in or to be incorporated in said member's food; and a palatable chewable form in which said inhibitor is consumed along with said palatable chewable form, or is delivered by leaching from said chew, which is not consumed, during mastication by said member being treated; liquid peroral dosage forms selected from the group consisting of solutions, suspensions, emulsions, inverse emulsions, elixirs, extracts, tinctures, and concentrates; and the above-recited solid dosage forms containing microencapsulated formulations of the active ingredient, which is incorporated into said solid dosage form.

11. (amended) A pharmaceutical composition as in Claims 5, 6, or 7 further comprising said anti-inflammatory selective COX-2 inhibitory compound in combination with one or more other therapeutically active agents independently selected from the group consisting ~~essentially~~ of:

A. anti-infectious agents comprising one or more antibiotic, antifungal, antiprotozoal, or antiviral therapeutic agents;

B. inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting ~~essentially~~ of:

1. NSAIDs;

2. H_1 -receptor antagonists;

3. kinin-B_1 - and B_2 -receptor antagonists;

4. prostaglandin inhibitors selected from the group consisting of PGD-, PGF- PGI_2 -, and PGE-receptor antagonists;

5. thromboxane A_2 (TXA2-) inhibitors;

6. 5- and 12-lipoxygenase inhibitors;

7. leukotriene LTC_4 -, LTD_4/LTE_4 -, and LTB_4 -inhibitors;

8. PAF-receptor antagonists;

9. gold in the form of an aurothio group together with one or more hydrophilic groups;

10. immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate;

11. anti-inflammatory glucocorticoids;

12. penicillamine;

13. hydroxychloroquine;

14. anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone, and benzbromarone;

C. therapeutic agents for the treatment of geriatric dogs comprising one or more members independently selected from the group consisting ~~essentially~~ of:

1. cognitive therapeutics to counteract memory loss and impairment;

2. anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure, and myocardial infarction, selected from the group consisting of:

a. diuretics;

b. vasodilators;

c. β-adrenergic receptor antagonists;

d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;

e. angiotensin II receptor antagonists;

f. renin inhibitors;

g. calcium channel blockers;

h. sympatholytic agents;

i. α_2-adrenergic agonists;

j. α-adrenergic receptor antagonists; and

k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

3. antineoplastic agents selected from:

a. antimitotic drugs selected from:

i. vinca alkaloids selected from:

[1] vinblastine, and

[2] vincristine;

4. growth hormone secretagogues;

5. strong analgesics;

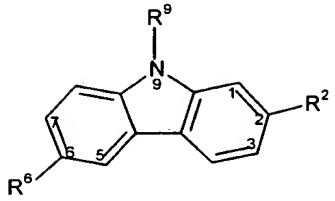
6. local and systemic anesthetics; and

7. H_2 -receptor antagonists, proton pump inhibitors, and other gastroprotective agents.

12. (Amended) A package suitable for use in commerce for the therapeutic treatment or prevention of pain and inflammation processes and diseases in a member of the species *Canis familiaris* in need of such treatment, comprising:

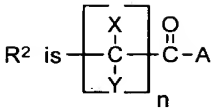
A. a suitable container optionally in the form of an outer package and an inner container removably housed therein;

B. a suitable dosage form, enclosed in said container, of an anti-inflammatory selective COX-2 inhibitory compound of the formula:



Formula (I):

wherein:



where A is hydroxy, (C_1 - C_4)alkoxy, amino, hydroxyamino, mono-(C_1 - C_2)alkylamino, di-(C_1 -C_2)alkylamino; one of X and Y is H and the other is (C_1 - C_2)alkyl; and n is 1 or 2;

R^6 is halogen, (C_1 - C_3)alkyl, trifluoromethyl, or nitro;

R^9 is H; (C_1 - C_2)alkyl; phenyl or phenyl-(C_1 - C_2)alkyl, where phenyl is optionally mono-substituted by fluoro or chloro; -C(=O)-R, where R is (C_1 - C_2)alkyl or phenyl, optionally mono-substituted by fluoro or chloro; or -C(=O)-O-R^1 , where R^1 is (C_1 - C_2)alkyl;

wherein (+)(*S*) enantiomer is present in amount of at least 75%; and all pharmaceutically acceptable salt forms, prodrugs and metabolites thereof which are therapeutically active for treating or preventing pain and inflammation; and

C. printed instructional and informational material associated with said container, which is attached to said container, enclosed in said container, or displayed as an integral part of said container, said instructional and informational material stating in words ~~which convey to a reader thereof of ordinary skill in the art~~ that said compound of Formula (I) comprising a therapeutic agent contained in said package, when administered to said member of the species *Canis* familiaris to be treated, effectively inhibits cyclo-oxygenase-2 (COX-2) induced at an existing or expected site of pain and inflammation in said dog, thereby treating or preventing said pain and inflammation which would otherwise result therefrom, while at the same time reducing or eliminating undesirable side effects associated with simultaneous inhibition of the activity of constitutive cyclo-oxygenase-1 (COX-1) by selectively inhibiting COX-2 activity with reference to COX-1 activity, wherein the selectivity ratio of COX-2 : COX-1 activity inhibition is at least 3 : 1 based on *ex vivo* inhibition levels in whole blood measured at a dose giving ≥ 80% COX-2 inhibition.

REMARKS

The claims are 1 to 26. Reconsideration is respectfully requested.

The Examiner requested that Applicants claim priority.

The Examiner requested that the Applicants submit an abstract for the present Application.

Without agreeing or disagreeing as to the propriety of the Examiner's request, but merely to expedite the prosecution of the present Application Applicants are including herewith an abstract and claim to priority.

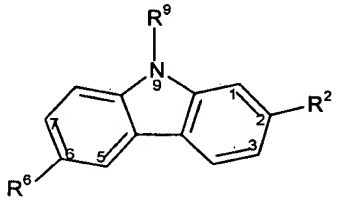
The Examiner requested the claims under 35 U.S.C. §112, second paragraph for the reasons enumerated in the text of the Official Action.

Without agreeing or disagreeing with the Examiner, but merely to expedite the prosecution of the present Application and to better define that which is considered to be the invention, Applicants have amended the claims and respectfully request that the §112 rejections be withdrawn.

The Examiner rejected the claims under 35 U.S.C. §102(b) as being anticipated by Berger, Holtsinger, and Vasseur as well as being obvious under 35 U.S.C. §103(a) in view of the same three references.

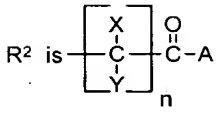
The Applicants believe that it would be useful to briefly review the key elements of the present invention as well as it attendant advantages. The present invention claims methods of treatment, pharmaceutical compositions, and packages for use in commerce for preventing or treating pain and inflammatory processes and diseases associated with the activity of inducible cyclo-oxygenase-2 (COX-2) in a member of the species *Canis familiaris*. The claimed methods, compositions, and packages treat the aforementioned conditions while at the same time reducing or eliminating undesirable side effects associated with simultaneous inhibition of the activity of constitutive cyclo-oxygenase-1 (COX-1) by selectively

inhibiting COX-2 activity with reference to COX-1 activity, wherein the selectivity ratio of COX-2 : COX-1 activity inhibition is at least 3 : 1 based on *ex vivo* inhibition levels in whole blood measured at a dose giving ≥ 80% COX-2 inhibition. Such methods, compositions, and packages provide for the administration to said member of the species *Canis familiaris* an amount therapeutically effective for treating pain and inflammation in accordance with the above-recited limitations, of an anti-inflammatory selective COX-2 inhibitory compound comprising a compound of the formula:



Formula (I)

wherein:



where A is hydroxy, (C_1 - C_4)alkoxy, amino, hydroxyamino, mono-(C_1 -C_2)alkylamino, di-(C_1 -C_2)alkylamino; X and Y are independently H or (C_1 - C_2)alkyl; and n is 1 or 2;

R^6 is halogen, (C_1 - C_3)alkyl, trifluoromethyl, or nitro;

R^9 is H; (C_1 - C_2)alkyl; phenyl or phenyl-(C_1 - C_2)alkyl, where phenyl is optionally mono-substituted by fluoro or chloro; -C(=O)-R, where R is (C_1 - C_2)alkyl or phenyl, optionally mono-substituted by fluoro or chloro; or -C(=O)-O-R^1 , where R^1 is (C_1 - C_2)alkyl;

where X and Y are different, the (-)(*R*) and (+)(*S*) enantiomers thereof; and all pharmaceutically acceptable salt forms, prodrugs and metabolites thereof which are therapeutically active for treating or preventing pain and inflammation.

As a result of utilizing these compounds in the above generic formula wherein the selectivity ratio of COX-2 : COX-1 activity inhibition is at least 3 : 1 based on *ex vivo*

inhibition levels in whole blood measured at a dose giving ≥ 80% COX-2 inhibition, pain and inflammatory processes and diseases associated with the activity of inducible cyclo-oxygenase-2 (COX-2) in a member of the species *Canis familiaris* is treated, while at the same time reducing or eliminating undesirable side effects associated with simultaneous inhibition of the activity of constitutive cyclo-oxygenase-1 (COX-1). One of the compounds within the species defined in the claims that meet the criteria set forth is carprofen. Pfizer Inc. currently markets a commercial product called RIMADYL that is encompassed by the claims of this Application. Therefore, the claims of this patent application are very important to my company.

None of the cited references render the claimed invention anticipated or obvious.

Berger relates to carbazoles that may have anti-inflammatory, analgesic, anti-rheumatic activity. Vasseur refers to the treatment of osteoporosis in dogs with carprofen. Holtsinger relates to the therapeutic efficacy of carprofen in canine degenerative joint disease.

None of the references cited by the Examiner disclose, teach, or suggest cyclo-oxygenase comprises two isoenzymes, a constitutive enzyme (COX-1) and an inducible enzyme (COX-2). Neither Berger nor Holtsinger include the word "cyclooxygenase." Vasseur only uses the term "cyclooxygenase" and does not use the terms "COX-1" or "COX-2."

The present invention, on the other hand, includes claim language that characterizes the compound of formula (I) as an anti-inflammatory selective COX-2 inhibitory compound. Without use of the terms "COX-1" or "COX-2," the references can not render the present invention obvious or anticipated.

None of the references cited by the Examiner disclose, teach, or suggest measuring the amount of COX-2 inhibition. As noted above, Berger and Holtsinger do not include the word

"cyclooxygenase" and Vasseur does not use the terms "COX-1" or "COX-2."

The claims of the present invention, on the other hand, not only use the terms "COX-1" or "COX-2," but also include claim language defining the level of COX-2 inhibition. One of the claim criteria requires measurement of COX-2 inhibition to determine if it is ≥ 80%. Without use of the terms "COX-1" or "COX-2," a reference can not refer to the measurement of the amount of COX-2 inhibition, thus, the references can not render the present invention obvious or anticipated.

None of the references cited by the Examiner disclose, teach, or suggest measuring for a selectivity ratio of COX-2:COX-1 activity inhibition. None of the references use the terms "COX-1" or "COX-2" or refer to the measurement of the amount of COX-2 inhibition.

The claims of the present invention, on the other hand, not only use the terms "COX-1" or "COX-2" and the measurement of the amount of COX-2 inhibition, but also include claim language defining selectivity ratio of COX-2:COX-1 activity inhibition based on *ex vivo* inhibition levels in whole blood to determine if it is at least 3 : 1. Without use of the terms "COX-1" or "COX-2" or referring to the measurement COX-2 inhibition, a reference can not refer to the determination of the selectivity ratio of COX-2:COX-1 activity inhibition and, thus, the references can not render the present invention obvious or anticipated.

None of the references cited by the Examiner disclose, teach, or suggest using compounds of formula I to treat pain or inflammation where the selectivity ratio of COX-2:COX-1 activity inhibition is at least 3:1 based on *ex vivo* inhibition levels in whole blood measured a dose giving ≥80% COX-2 inhibition. None of the references use the terms "COX-1" or "COX-2"; or refer to the measurement COX-2 inhibition or the determination of the selectivity ratio of COX-2:COX-1 activity inhibition.

The claims of the present invention, on the other hand, not only includes the terms "COX-1" or "COX-2," the measurement COX-2 inhibition, and the determination of the selectivity ratio of COX-2:COX-1 activity inhibition but also includes criteria based upon this data to define those compounds of formula (I) within the scope thereof. According to the claims, the anti-inflammatory selective COX-2 inhibitory compound of formula (I) should have a selectivity ratio of COX-2 : COX-1 activity inhibition is at least 3 : 1 based on *ex vivo* inhibition levels in whole blood measured at a dose giving ≥ 80% COX-2 inhibition. This criterion defines those compounds of formula (I) within the scope of the claims. Without use of the terms "COX-1" or "COX-2" or referring to the measurement COX-2 inhibition or the determination of the selectivity ratio of COX-2:COX-1 activity inhibition, a reference can not be said to refer to a COX-2 : COX-1 activity inhibition of at least 3 : 1 based on *ex vivo* inhibition levels in whole blood measured at a dose giving ≥ 80% COX-2 inhibition and, thus, the references can not render the present invention obvious or anticipated.

Without such teaching or suggestion, the invention of the present claims is patentable in view the cited references.

Furthermore with regard to claims 4 and 11, in addition to the above arguments, these claims are patentable over the cited references for additional reasons. None of the cited references disclose, teach, or suggest the combination of the compounds of formula I as defined in the claims in combination with any other therapeutically active agents. Each of the cited references relates to carprofen alone. Neither Berger, Vasseur, nor Holtsinger refer to combining carprofen with another therapeutic compound. Without such teaching or suggestion, claims 4 and 11 are patentable in view of the cited references.

Applicant, therefore, respectfully request that the claims

be allowed and the application passed on to issue.

Respectfully submitted,

Dated: Oct. 4, 2021

Grover F. Fuller Jr

GROVER F. FULLER JR.
ATTORNEY for Applicants
Reg. No. **31,760**

Pfizer Inc.
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212) 573-**1390**